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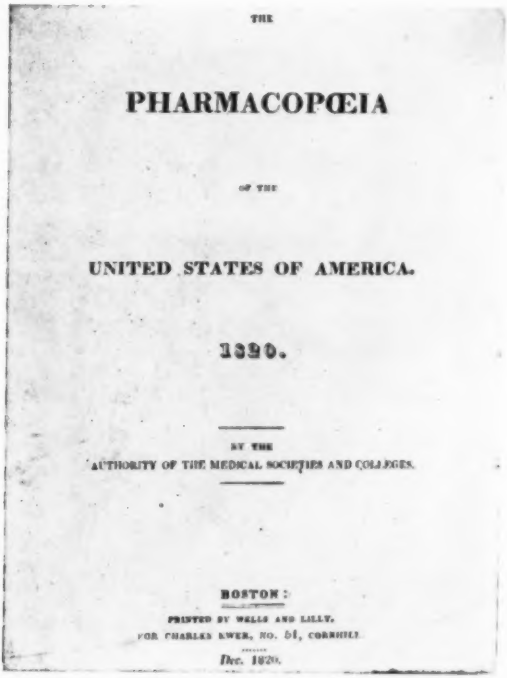

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E D I T O R I A L

THE 1960 UNITED STATES PHARMACOPEIAL CONVENTION

THE call for delegates has been sent to those institutions and organizations entitled to representation at the 1960 Pharmacopeial Convention. This in itself is not unusual since similar conventions have been held regularly every decade as part of the Pharmacopeial program. A change in the Constitution and By-Laws makes this Convention quite different, however, and unless this is anticipated and clearly understood it might seriously hamper the functioning of the work of revision for both U. S. P. XVII and XVIII.

In accordance with the revised Constitution and By-Laws, each organization entitled to representation is now privileged to send only *one* delegate to the Convention rather than three as heretofore. On the surface, this seems like a perfectly reasonable change since it does give each group having an interest in drug standards the opportunity of representation and a hand in the selection of the new Committee of Revision, the officers, and the Board of Trustees. What is not clearly established is whether this new plan will provide for a better selection of those to whom the Pharmacopeia will be entrusted for the next decade. The answer to this question depends almost entirely on how judiciously that one person who is to be the delegate for a given organization or institution is selected.

It is a high honor to be appointed the official delegate representing, let us say, a college or a professional society at the United States Pharmacopeial Convention. One has the privilege of meeting in Washington with a very distinguished group. For a full decade, his name is published as the official delegate representing his institution or organization. There is also some inner satisfaction in being given the task of voting for those who are to constitute the Revision Committee and the Board of Trustees. So great is this psychic return that there is the built-in risk that the one selected for this high honor will not be a scientist or one who is quite familiar with the aptitudes and capabilities of pharmaceutical and medical experts. What is

more likely is that the delegate will be one who is high in the "political" echelons of the pharmaceutical or medical professions. While such delegates are fully qualified to select the officers and Board of Trustees to manage the affairs of the Pharmacopeia for the next decade, it is not certain that they possess the competence to judge the relative capabilities of those scientists who must make up the Committee of Revision. This has always been the case but, in the days when each organization was entitled to three delegates, the conditions were more conducive to ample representation of scientists at the Convention.

The task of revising the Pharmacopeia has become exceedingly complex and one cannot help but be concerned over what might happen to the Pharmacopeia if the Committee of Revision, as selected, did not include a rather sizable number of topnotch experts. There is no reason to believe that the work of preparing monographs will not continue to become more complicated and exacting each passing year. After all, the Pharmacopeia reflects science of our day and no-one can deny that every field of science seems to have burgeoned into a colossal structure.

It is the purpose of this editorial to pointedly suggest and even urge those whose responsibility it is to select or appoint a delegate to the Pharmacopeial Convention that they choose one whose achievements in one of the pharmaceutical or medical sciences have made him outstanding. In all likelihood, such an individual can best judge the suitability of candidates for positions on the Committee of Revision. We have reason to be proud of our Pharmacopeia and its past record. To a large measure, how well the delegates to the 1960 Convention are selected will determine whether the Pharmacopeia will continue to merit the respect of government, industry, and our healing professions.

L. F. Tice

HONEY AS A VEHICLE FOR MEDICINAL PREPARATIONS *

By Nathan Rubin, Alfonso R. Gennaro, Catherine N. Sideri, and Arthur Osol

HONEY has been used in the formulation of medicinals since ancient times, but comparatively little scientific information concerning its suitability as a vehicle for medicinal products is available. The object of this investigation, performed over a period of two years, was to obtain such information. Twenty-one different types of liquid medicinal preparations were studied to find out if honey may advantageously replace part or all of the glycerin and/or syrup usually used in these liquids. In such a study the problem of the stability of the active ingredient(s) of a preparation containing honey is of primary importance. Because sugar-containing products may be susceptible to deterioration by microbiological organisms, this problem too is very important. And, taste is increasingly a matter of concern in evaluating medicinals. Finally, if honey is useful as an ingredient of a medicinal product, its producer must be assured that he may obtain the same, essentially uniform, honey each time he purchases it, for which reason quality specifications must be established for honey suitable for use in medicinal preparations. All these problems were investigated in the course of this study.

Stability of Various Medicinal Formulations

General

One of the variables investigated in these experiments was the effect of variation of pH on the different honey-containing vehicles. Honey is naturally acid in reaction, having a pH of approximately 3.7. When its pH is raised, two deleterious effects are observed: the honey becomes darker, and its aroma is markedly altered, becoming somewhat unpleasant; these effects are especially pronounced when the pH is above 7. The changes are largely attributable to degradation of the dextrose and levulose in honey.

* A contribution from the School of Chemistry, Philadelphia College of Pharmacy and Science.

A report of work done under contract with the U. S. Department of Agriculture and authorized by the Research and Marketing Act of 1946. The contract is being supervised by the Eastern Utilization Research and Development Division of the Agricultural Research Service.

Another of these variables investigated was the effect of temperature on stability; data were obtained at room temperature, at 37°, and some at 50°. When stored at 50°, honey containing 10 per cent of added water (corresponding to the concentration of water in some of the vehicles) developed a brownish-black precipitate, from which behavior the unfavorable effect of elevated temperatures is apparent.

Honey suitable for use as a vehicle for medicinal products should be of the commercial variety designated as "heat-processed and filtered". With regard to clarity, some producers supply honey that may be used without further filtration; however, not all honeys described as having been filtered have acceptable clarity (though it should be noted that even the clearest honeys show the turbidity of colloidal solutions). The advantage of using honey that requires no filtration becomes apparent when this cumbersome operation does have to be performed, for which a suitable filter aid (0.5 to 0.75 per cent of Celite Standard Super Cel is satisfactory) is required and the filtration must be performed under pressure (10 to 14 lbs. per sq. in.). When adequately filtered honey is available for use in making solutions of water-soluble medicinal agents, the latter should be dissolved in the required amount of warm or hot water, the solution filtered and then mixed with the honey; this procedure suffices to give a clear solution.

Ferrous Sulfate Formulations

Several formulations, each containing the proportions of ferrous sulfate and citric acid specified in the formula for U. S. P. Ferrous Sulfate Syrup but differing in having as the vehicle a mixture of honey and water and in not containing peppermint spirit, were prepared. All these were completely stable, whether stored at 25° or 37°, as determined by periodic titrations with 0.1 *N* ceric sulfate during the period of observation of 11 months. All the solutions were very palatable; the following formula yields, in our opinion, a product with the most desirable viscosity.

Ferrous Sulfate	40	Gm.
Citric Acid, hydrous	2.1	Gm.
Water	210	Gm.
Honey *	1150	Gm.

* In order to know the exact composition of our preparations the ingredients were in most instances weighed; this formula yields approximately 1000 ml. of solution.

To prepare this solution, the ferrous sulfate and citric acid were dissolved in water with the aid of heat, the solution filtered, and mixed with the honey. The pH of the finished product is 2.6.

Sulfonamide Suspensions

Of the several formulations prepared and tested for stability, the one of the following composition seemed to us to have the most desirable physical characteristics. Settling of the suspended solids is slight and slow. Compared with three commercially available sulfonamide suspensions, it ranked first in the taste preference of a "panel" of 25 students. During 10 months of observation, the total sulfonamides content, as determined by titration with 0.1 *M* sodium nitrite, decreased only approximately 4 per cent.

Sulfadiazine (Calcomites®)	42	Gm.
Sulfamerazine (Calcomites®)	42	Gm.
Sulfamethazine (Calcomites®)	42	Gm.
Sodium Citrate	6.7	Gm.
Acacia	6.7	Gm.
Methylparaben	0.5	Gm.
Propylparaben	0.11	Gm.
Alcohol	17	Gm.
Glycerin	170	Gm.
Honey	950	Gm.
Water, sufficient to make a total of	1350	Gm.*

The suspension was prepared as follows: (1) the acacia was wetted with water, the remainder of which was used to dissolve the sodium citrate; (2) the parabens were dissolved in alcohol; (3) the sulfonamides were mixed with the glycerin and honey; (4) to the suspension of sulfonamides was added the solution of parabens; (5) to the mixture obtained in (4) the acacia and sodium citrate solutions were added, alternately; (6) the product was passed through a colloid mill. The pH of the finished suspension is 5.9. In place of the parabens, 0.05 per cent (w/v) of sorbic acid may be used as the preservative.

* This corresponds to about 1000 ml. of suspension, each 4 ml. of which contains about 0.5 Gm. of mixed sulfonamides.

Preparations for Cough

Honey has long been used, especially in Europe, as an ingredient of preparations intended for treatment of cough, for which purpose it is well suited. We prepared several formulations of ingredients employed in contemporary products, and found two to have desirable characteristics which gave no physical evidence of change on standing fourteen (14) months (attempts to develop satisfactory quantitative procedures for the principal ingredients were unsuccessful). The preparations were very palatable. Clinical use of the products indicated them to have good antitussive action, which showed no evidence of diminution on storage.

The following are the formulas of the two preparations:

Dihydrocodeinone Bitartrate	0.32	Gm.
Pyrilamine Maleate	2.4	Gm.
Potassium Guaiacolsulfonate	32	Gm.
Sodium Citrate	16	Gm.
Citric Acid	16	Gm.
Sorbic Acid	0.5	Gm.
Water	160	Gm.
Honey	1150	Gm.

The solid ingredients were dissolved in about 140 Gm. of water with the aid of gentle heat, the solution filtered and the filter washed with the remainder of the water, and the filtrate and washings mixed with the honey.

Codeine Sulfate	2.1	Gm.
Promethazine Hydrochloride	1.05	Gm.
Potassium Guaiacolsulfonate	8.4	Gm.
Sodium Citrate	37.5	Gm.
Citric Acid	12.5	Gm.
Ipecac Fluidextract	2.3	ml.
Chloroform	4.1	Gm.
Water	155	Gm.
Glycerin	190	Gm.
Honey	940	Gm.

The water solution of the solid ingredients was prepared as for the preceding preparation. This solution was added to a mixture of

the fluidextract, glycerin and honey and, when it had cooled to room temperature, the chloroform was incorporated. Filtration of the product, under pressure, and using filter aid (see above, under *General*), was found to be desirable.

Terpin Hydrate Formulations

Several preparations containing terpin hydrate were made. A variant of N. F. Terpin Hydrate Elixir, in which honey replaces the syrup and part of the glycerin, was found to be highly palatable and to remain clear on standing. The formula for this is:

Terpin Hydrate	16.9	Gm.
Sweet Orange Peel Tincture	20	ml.
Alcohol	425	ml.
Honey	400	ml.
Glycerin	200	ml.
Water, sufficient to make	1000	ml.

This elixir was made in the same manner as the N. F. elixir. After standing for several weeks a fine gelatinous precipitate formed but after removing this by filtration the product remained clear indefinitely.

Barbiturate Preparations

Several elixirs containing phenobarbital or pentobarbital in vehicles employing honey were prepared. While a few of the solutions remained fairly stable for six months, in our judgment none offered any advantage over the respective official preparations.

Vitamin Formulations

The stability of thiamine hydrochloride, riboflavin (as sodium riboflavin-5′-phosphate), cyanocobalamin, and ascorbic acid, separately, was studied in a vehicle of honey containing 10 per cent by volume of added water, at pH values ranging from 3.5 to 7.4, at room temperature and 37°, and in clear and brown bottles. Only riboflavin was acceptably stable, when stored in brown bottles, in the entire pH range, and at either temperature; decomposition at 77 days was of the order of 2 to 5 per cent. When stored in clear bottles, 25 to 30 per

cent of the riboflavin was decomposed in 6 days. Thiamine hydrochloride underwent considerable decomposition, and cyanocobalamin deteriorated very rapidly. Ascorbic acid was less stable in honey than in simple syrup; some stabilization was effected by adding 0.05 per cent of tetrasodium ethylenediamine tetraacetate, but not to a sufficient degree. In a solution containing both thiamine and riboflavin, the latter had a stabilizing effect on the former and both vitamins deteriorated to an extent of 2 to 5 per cent in the 63-day period of observation. Other mixtures did not show desirable stability characteristics. For extemporaneous compounding of these vitamins, honey may be used as a vehicle, if the preparation is stored in a brown bottle, and if used within a period of about 10 days.

Aspirin Preparations

Various combinations of aspirin with honey and other liquids were investigated in an attempt to prepare at least a suspension of acceptable stability. The most stable product we were able to obtain showed about 5 per cent hydrolysis of aspirin in two days, and approximately 12 per cent in five days (the analytical procedure was based on measurement of the intensity of color produced with salicylic acid on addition of ferric ion, the observation being made at 525 millimicrons in a spectrophotometer). Its formula, which represents approximately 2 grains of aspirin per 5-ml. teaspoonful, is:

Aspirin	28.8	Gm.
Alcohol	40	ml.
Glycerin	200	ml.
Honey, sufficient to make	1000	ml.

The aspirin was triturated with the alcohol, this mixture added, with constant stirring, to the glycerin, and this mixed with the honey. The pH of the suspension is 3.6.

Other Preparations

Variants of several official products, in which honey was incorporated in the respective vehicles, were prepared, these being: Compound Glycerophosphates Elixir; Iron and Ammonium Acetate Elixir; Iron, Quinine and Strychnine Elixir; Compound Opium and

Glycyrrhiza Mixture; Pepsin and Rennin Elixir; Compound Pepsin Elixir. These preparations were either not as palatable or stable, or both, as the official products.

Preservation Against Microorganisms

Because honey diluted with water is subject to deterioration by microbiological growth, the investigation of the effects of various preservatives is obviously of importance in evaluating the utility of honey as a vehicle for medicinals. Solutions containing various proportions of honey and water were inoculated with different organisms, and the effect of sorbic acid (0.05 and 0.1 per cent), sodium benzoate (0.1 per cent), and a mixture of methylparaben (0.2 per cent) and propylparaben (0.05 per cent) was determined. Sorbic acid in 0.05 per cent (w/v) concentration prevented fungous growth and spoilage; in 0.1 per cent concentration precipitation of some of the sorbic acid occurred in solutions containing a high proportion of honey. Sorbic acid may be incorporated by first dissolving it in hot water, then mixing this solution with honey. Potassium sorbate, which is more soluble in water, may be used in place of sorbic acid. With sodium benzoate (0.1 per cent), growth was observed in some cases. The mixture of parabens was not consistent in preventing growth; in part this may have been due to separation from the solutions of some of the propylparaben, crystals of which were identified by their infrared absorption spectrum. These experiments indicated sorbic acid to be the most effective preservative, and it appears advisable to include it in any preparation containing honey and water.

Quality Specifications

While standards for honey are provided in the monograph for it in the *National Formulary*, these standards will not insure constancy of different lots of honey, which is essential if uniformity of different batches of a product in which honey is an ingredient is to be maintained. The following specifications are more restrictive, and provide for greater uniformity of honey intended for use in medicinals.

General Description

Honey is the nectar of floral exudations of plants gathered and stored in the comb by honey bees, *Apis mellifera* Linné (Fam.

Apidae). It must be heat-treated for 30 minutes at 140° F. to 160° F. (maximum) and free from foreign substances such as parts of insects, leaves, etc., but may contain pollen grains. When graded according to the United States Standards for Grades of Extracted Honey (18 F. R. 52.1391-52.1404), it must be classified as "U. S. Choice" or "U. S. Fancy".

Moisture Content

Not more than 18.6 per cent, by weight. This corresponds to a refractive index ($n_D20°$) of not less than 1.4900, and a specific gravity (20°/20° C.) of not less than 1.4129.

Optical Rotation

Honey is levorotatory at 20° C.

Residue on Ignition

Not more than 0.40 per cent.

Artificial Honey

Introduce 10 ml. of a mixture of equal volumes of honey and water into a test tube and add 5 ml. ether. Shake gently and allow to stand until the ether layer is clear. Transfer 2 ml. of this clear ether solution to a small test tube and add a large drop of freshly prepared resorcinol solution (1 Gm. resorcinol in 100 ml. of hydrochloric acid of sp. gr. 1.18-1.19). A cherry-red color appearing within one minute indicates the presence of artificial honey. Yellow to salmon shades have no significance.

Acidity

A solution of 10 Gm. of honey in 50 ml. of water requires not more than 5.0 ml. of 0.1 N sodium hydroxide for neutralization, using phenolphthalein as indicator.

Color

Shall not be darker than Light Amber, when determined by use of the U. S. D. A. permanent glass color standards.

Floral Type

Many floral types of honey are available, including those designated as follows: Alfalfa, Basswood, Clover, Cotton, Eucalyptus, Florida Orange, Mesquite, Palmetto, Sage, Star Thistle, Tulip Poplar, and others. The choice of floral type should be left to the discretion of the manufacturer of the product in which honey is used (clover honey was used in most of the formulations reported in this paper). Regardless of the floral type selected, the honey should meet all of the requirements proposed.

Packaging and Storage

Honey should be stored in well-closed containers, and the temperature should not exceed 90° F. for a prolonged period. Honey that has granulated may be liquefied in its container by heating at a temperature not over 160° F. for 30 minutes, with occasional stirring.

Acknowledgment

The authors express their appreciation to Dr. Jonathan W. White, Jr., of the Eastern Utilization Research and Development Division of the Agricultural Research Service for his many helpful suggestions and other aid during this investigation.

A PHARMACOLOGIC STUDY OF THE POTENTIATION OF THE ACTIVITY OF VARIOUS ANTIHYPERTENSIVE DRUGS *

By Sidney Goldstein ** and G. Victor Rossi

POTENTIATION has been defined as the phenomenon whereby the combined action of two drugs is greater than that which can be anticipated from the sum of their individual actions. Ever since the beginning of medical practice, drugs have been combined in an attempt to surpass the beneficial effects obtainable by administration of the separate components.

Burgi (1) in 1910 was the first investigator to critically study the effect of drug combinations. He formulated the following concept: "In combining drugs with the same end-effect, the resulting activity is additive when the sites of action of the components are identical, and superadditive if these are different". In recent years, considerable attention has been devoted to attempts to elucidate the mechanism of drug potentiation. Veldstra (2) in 1956 presented a comprehensive review of various aspects of synergism and potentiation which have been demonstrated to occur among many classes of pharmacodynamic agents, and offered an explanation of these phenomena. Although a number of unifying concepts have been advanced, it appears unlikely that all forms of drug potentiation involve a common mechanism.

Several synthetic compounds of diverse structure, which exert minimal pharmacologic effects when administered alone, have been shown to prolong the action and, in some cases, enhance the intensity of action of a variety of drugs. Among such agents are SKF 525-A (beta-diethylaminoethyl diphenylpropyl acetate), which has been most extensively studied; Lilly 18947 (2,4-dichloro-6-phenylphenoxyethyl diethylamine hydrobromide); NDR A-1358 (2-[1-phenylethyl]-4-

* From the LaWall Memorial Laboratory of Pharmacology and Biochemistry, Philadelphia College of Pharmacy and Science, Philadelphia 4, Pa.

** Abstracted from an investigation submitted by Sidney Goldstein to the Graduate School of the Philadelphia College of Pharmacy and Science in partial fulfillment of the requirements for the degree of Doctor of Science. Present address: Eaton Laboratories, Norwich, N. Y.

pentenamide), and NDR A-2435 (2-[p-chlorobenzyl]-4-pentenoic acid hydrazide).

The purpose of this investigation was to evaluate the effects of these four agents (SKF 525-A [1], Lilly 18947 [2], NDR A-1358 [3], and NDR A-2435 [3]) on the blood pressure reducing activity of a group of hypotensive drugs having diverse sites and modes of depressor action. This study was conducted with unanesthetized chronic hypertensive rats and unanesthetized normotensive dogs. Several aspects of this investigation formed the basis of a previous report (3).

Methods

Hypertension was induced in male Sherman rats, weighing approximately 135 gm., by applying a figure-8 ligature made with coarse thread, to one kidney stripped of fascia; two weeks later, the contralateral kidney was removed and a 75 mg. pellet of desoxycorticosterone acetate [4] was implanted subcutaneously in the shoulder area. This procedure was selected on the basis of the production of persistent, moderately severe hypertension in a high percentage of animals operated upon, coupled with a high rate of survival. The hypertensive rats were maintained in constant temperature quarters with free access to Rockland Rat Diet and tap water.

Blood pressure was determined in the unanesthetized rat by the photoelectric tensometer method (4). Only rats developing sustained systolic blood pressure of 170 mm. Hg, or greater, were employed. The animals were separated into experimental groups with comparable blood pressures. In the studies performed with rats, all drugs were injected intraperitoneally in a solvent consisting of a 1:1:2 ratio of propylene glycol, ethanol, and distilled water. When used, the potentiating agents were administered in a concentration of 20 mg./Kg. one hour before injection of the depressor drugs (except for one phase of this study, during which the potentiating agents were administered after the fourth hour blood pressure determination).

Systolic blood pressure was estimated in trained unanesthetized normotensive dogs by an indirect method which employed a Visoton in

[1] Generously supplied by Smith Kline and French Laboratories, Philadelphia, Pa.

[2] Generously supplied by Eli Lilly and Company, Indianapolis, Ind.

[3] Generously supplied by National Drug Company, Philadelphia, Pa.

[4] Generously supplied by Schering Corporation, Bloomfield, N. J.

TABLE I

Summary of the effect of various potentiating agents on the depressor activity of six hypotensive drugs in hypertensive rats

Hypotensive Drug (H.D.)	SKF 525-A and H.D. / H.D. alone	Ratio	Lilly 18947 and H.D. / H.D. alone	Ratio	NDR A-1358 and H.D. / H.D. alone	Ratio	NDR A-2435 and H.D. / H.D. alone	Ratio
Reserpine 0.01 mgm./kgm.	1452* / 512	2.4	1063 / 588	1.8	1463 / 586	2.5	1327 / 604	2.2
Rescinnamine 0.01 mgm./kgm.	1205 / 612	2.0	1254 / 610	2.1	1139 / 597	1.9	1133 / 595	1.9
Hydralazine 0.4 mgm./kgm.	1470 / 706	2.1	1348 / 730	1.9	1566 / 721	2.5	1760 / 714	2.2
Mecamylamine 0.2 mgm./kgm.	1028 / 535	1.9	1098 / 522	2.1	1001 / 532	1.9	1018 / 548	1.9
2-(N,N-diallylcarbamylmethyl)-aminomethyl-1,4-benzodioxan 0.5 mgm./kgm.	940 / 461	2.0	1048 / 451	2.3	1013 / 502	2.0	886 / 495	1.8
Mannitol Hexanitrate 0.4 mgm./kgm.	720 / 350	2.1	631 / 367	1.7	610 / 328	1.9	622 / 332	1.9

* Sum of the reductions in systolic blood pressure (mm. Hg) determined 1, 2, 4, and 6 hours after intraperitoneal injection of the hypotensive drug.

N = 10 in each group.

combination with an Infraton Pickup (5). This technique involves the use of a sensitive capacitor microphone (Infraton) as a detector of either arterial pulse waves or sounds, or both, which produce characteristic patterns on the long persistence oscilloscope screen of the Visoton. The Infraton Pickup, secured on the dog's ankle distal to a pediatric sphygmomanometer cuff, replaces the stethoscope in the auscultatory determination of blood pressure. In the experiments performed with dogs, the hypotensive drugs were administered intravenously and the potentiating agents were injected intraperitoneally.

An attempt was made to select hypotensive drugs representative of various sites and mechanisms of depressor action. The six drugs employed in this study were: reserpine, rescinnamine, hydralazine (Apresoline); mecamylamine (Inversive); 2-(N,N-diallylcarbamylmethyl)-aminomethyl-1,4-benzodioxan (NDR A-2275, an experimental adrenergic blocking agent), and mannitol hexanitrate.

In the performance of each experiment, one group was treated with both a potentiating agent and a hypotensive drug. A second group of equal number was injected with only the solvent prior to administration of the hypotensive drug. The systolic blood pressure of every animal was measured before and 1, 2, 4, and 6 hours after drug treatment. These concurrent trials, (i.e., hypotensive drug alone and hypotensive drug in combination with a potentiating agent), which constituted a single experiment, were evaluated individually by analysis of variance (6).

Results

Under the conditions of this investigation, the blood pressures of unanesthetized chronic hypertensive rats ($N = 20$) and normotensive dogs ($N = 12$) receiving only intraperitoneal injections of solvent (described in the section on methods) remained very stable when measured 1, 2, 4, and 6 hours after treatment. Administration of 20 mg./Kg. of either SKF 525-A, Lilly 18947, NDR A-1358, or NDR A-2435 alone produced neither detectable changes in activity nor significant effect on systolic blood pressure during the six-hour experimental period in hypertensive rats ($N = 20$ in each case) or normotensive dogs ($N = 6$).

Intraperitoneal injection of either 10 mcg./Kg. of reserpine, 10 mcg./Kg. of rescinnamine, 0.4 mg./Kg. of hydralazine, 0.2 mg./Kg.

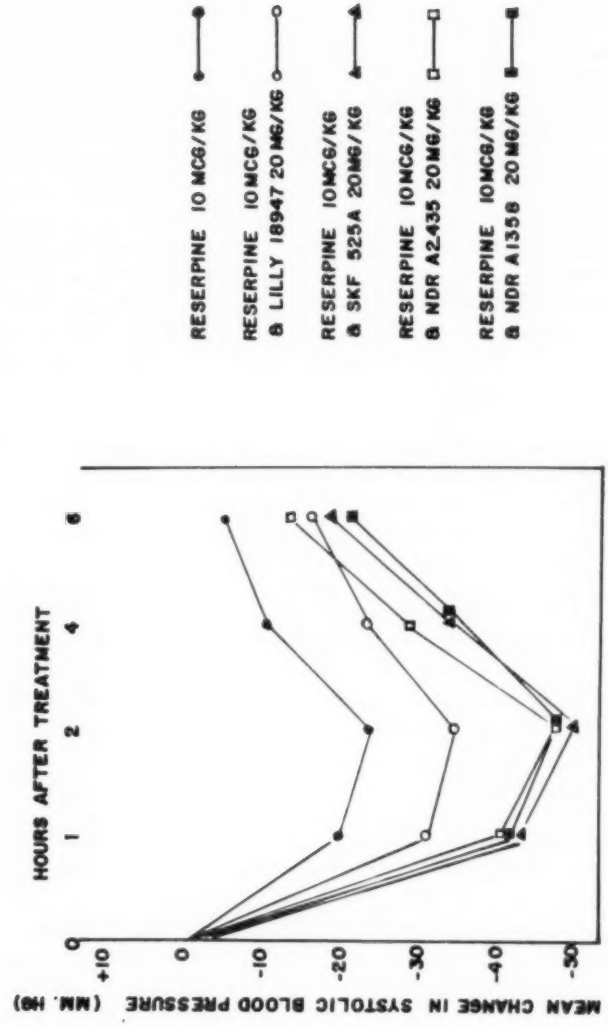
RESERPINE 10 MCG/KG
RESERPINE 10MCG/KG & LILLY 18947 20 MG/KG
RESERPINE 10MCG/KG & SKF 525A 20MG/KG
RESERPINE 10MCG/KG & NDR A2435 20MG/KG
RESERPINE 10MCG/KG & NDR A1358 20 MG/KG
HOURS AFTER TREATMENT
1
2
4
6
0
+10
0
-10
-20
-30
-40
-50
MEAN CHANGE IN SYSTOLIC BLOOD PRESSURE (MM. HG)

FIGURE 1

of mecamylamine, 0.5 mg./Kg. of the benzodioxan compound (NDR A-2275), or 0.4 mg./Kg. of mannitol hexanitrate, one hour after administration of 20 mg./Kg. of either SKF 525-A, Lilly 18947, NDR A-1358, or NDR A-2435 to hypertensive rats resulted in a reduction of blood pressure which was significantly ($P<0.001$) greater in each case than the response elicited by the hypotensive drug given alone. The sum of the reductions in systolic blood pressure determined at the 1, 2, 4, and 6 hour test periods in rats pretreated with a potentiating agent is compared, in Table 1, with the total blood pressure reduction similarly determined in animals injected only with the hypotensive drug. Table 1 also lists the "potentiation ratio", calculated by dividing the total drop in blood pressure occurring in the pretreated group by the total reduction recorded in the group which did not previously receive a potentiating agent. Figure 1 illustrates the results obtained with 10 mcg./Kg. of reserpine alone and in combination with each of the four potentiating agents.

The effect of the four potentiating agents on the blood pressure reducing activity of subthreshold doses of six hypotensive drugs was also investigated in hypertensive rats. Significant blood pressure reductions occurred after the injection of 2 mcg./Kg. of reserpine, 2 mcg./Kg. of rescinnamine, 60 mcg./Kg. of hydralazine, 40 mcg./Kg. of mecamylamine, 60 mcg./Kg. of NDR A-2275, or 40 mcg./Kg. of mannitol hexanitrate in animals which had been administered 20 mg./Kg. of SKF 525-A, Lilly 18947, NDR A-1358, or NDR A-2435 one hour previously. The doses of the hypotensive drugs listed above elicited no detectable alteration in blood pressure when administered to hypertensive rats pretreated only with solvent. Figure 2 graphs the changes in blood pressure in hypertensive rats following the intraperitoneal injection of 2 mcg./Kg. of reserpine alone and one hour after administration of each of the four potentiating agents. Comparable effects were observed with all of the drug combinations outlined above.

An investigation was made of the effect on blood pressure of hypertensive rats of the administration of SKF 525-A, Lilly 18947, NDR A-1358, and NDR A-2435 after the depressor response to hypotensive drugs had largely terminated. It was observed that these potentiating agents were capable of reinducing a significant blood pressure reduction when injected after the depressor activity of each hypotensive drug had clearly passed its maximum. A second fall in

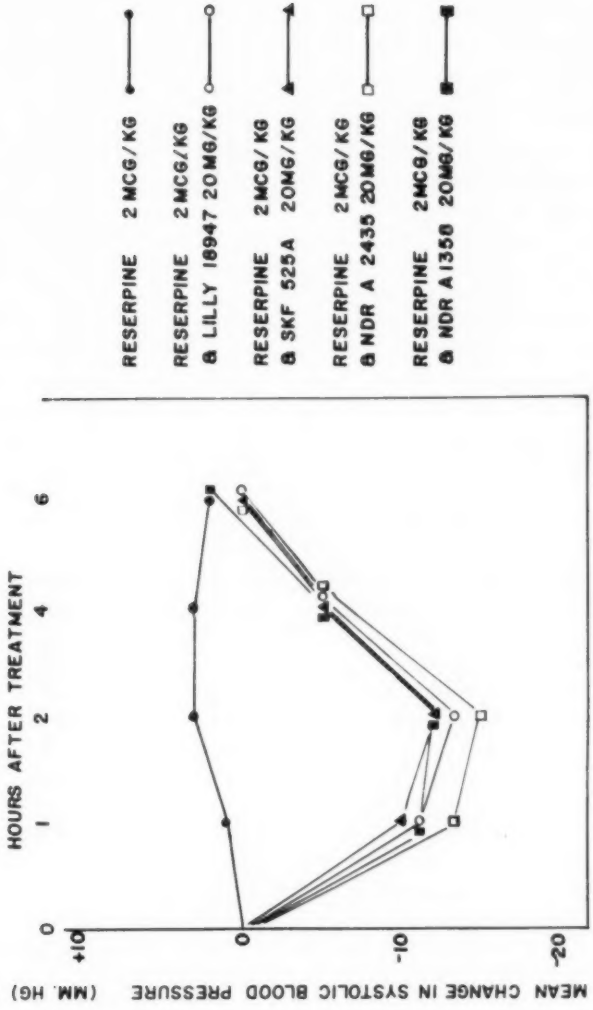
RESERPINE 2 MCG/KG
RESERPINE 2MCG/KG
LILLY 18947 20MG/KG
RESERPINE 2MCG/KG
SKF 525A 20MG/KG
RESERPINE 2MCG/KG
NDR A 2435 20MG/KG
RESERPINE 2MCG/KG
NDR A1350 20MG/KG
HOURS AFTER TREATMENT
0
1
2
4
6
MEAN CHANGE IN SYSTOLIC BLOOD PRESSURE (MM. HG)
+10
0
-10
-20

FIGURE 2

systolic blood pressure, which generally exceeded the initial response, was uniformly observed following intraperitoneal injection of 20 mg./Kg. of SKF 525-A, Lilly 18947, NDR A-1358, or NDR A-2435 immediately after the fourth-hour blood pressure measurement in rats which had previously received 10 mcg./Kg. of reserpine, 10 mcg./Kg. of rescinnamine, 0.4 mg./Kg. of hydralazine, 0.2 mg./Kg. of mecamylamine, 0.5 mg./Kg. of NDR A-2275, or 0.4 mg./Kg. of mannitol hexanitrate. The responses obtained with SKF 525-A administered both one hour before and four hours after injection of 10 mcg./Kg. of reserpine, and SKF 525-A administered only four hours after reserpine treatment, as presented in Figure 3, are typical of the results obtained with similar combinations of the four potentiating agents and other hypotensive drugs.

A moderate reduction in blood pressure was found to occur when either SKF 525-A, Lilly 18947, NDR A-1358, or NDR A-2435 was administered four hours after injection of a subthreshold dose of the six hypotensive drugs (previously listed). A resumption of depressor activity was also observed following the fourth-hour administration of potentiating agents to hypertensive rats pretreated with the same agents prior to injection of hypotensive drug. Figure 4, which depicts the responses obtained with SKF 525-A and subthreshold doses of reserpine, is representative of this series of experiments.

Several of the types of investigations performed with hypertensive rats were also conducted with normotensive dogs and, in all cases, qualitatively similar results were obtained. Intravenous administration of 0.3 mg./Kg. of hydralazine, 0.3 mg./Kg. of mecamylamine, 0.4 mg./Kg. of the benzodioxan compound NDR A-2275, or 0.3 mg./Kg. of mannitol hexanitrate one hour after intraperitoneal injection of 20 mg./Kg. of SKF 525-A, Lilly 18947, NDR A-1358, or NDR A-2435 to normotensive unanesthetized dogs resulted in a significantly greater reduction of systolic blood pressure than that produced by the hypotensive drug administered alone. Data obtained with 0.3 mg./Kg. of hydralazine alone and in combination with each of the four potentiating agents are illustrated in Figure 5. Reserpine and rescinnamine were not included in this series due to the marked sedative effect which accompanied administration of these alkaloids in doses sufficient to elicit a significant depressor response in unanesthetized dogs. However, subthreshold doses of reserpine and rescinnamine (0.2 mg./Kg.) resulted in a moderate reduction of

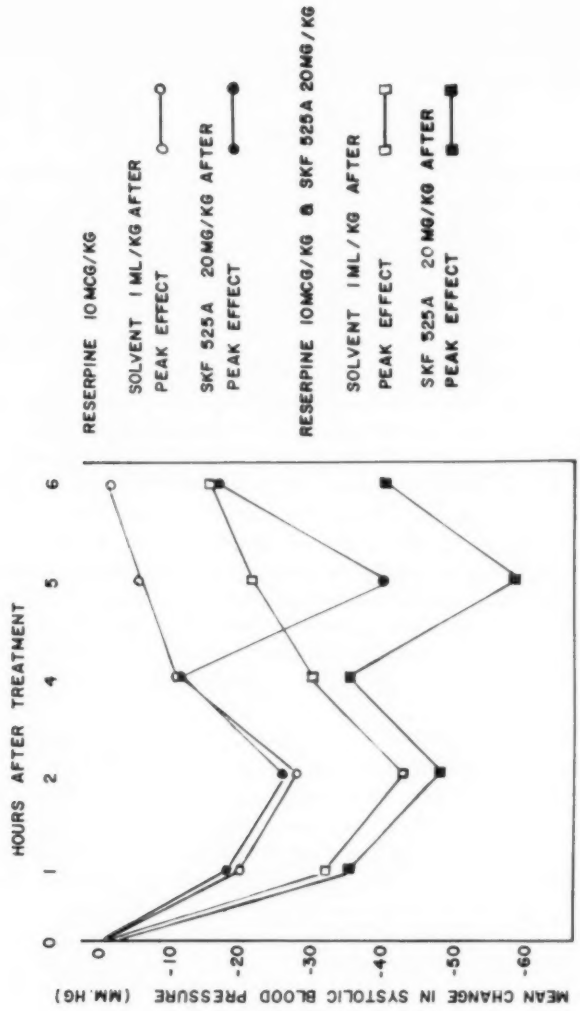
RESERPINE 10MCG/KG
SOLVENT 1 ML/KG AFTER
PEAK EFFECT
SKF 525A 20MG/KG AFTER
PEAK EFFECT
RESERPINE 10MCG/KG & SKF 525A 20MG/KG
SOLVENT 1 ML/KG AFTER
PEAK EFFECT
SKF 525A 20 MG/KG AFTER
PEAK EFFECT
HOURS AFTER TREATMENT
0
1
2
4
5
6
MEAN CHANGE IN SYSTOLIC BLOOD PRESSURE (MM. HG)
0
-10
-20
-30
-40
-50
-60

FIGURE 3

blood pressure when administered to normotensive dogs one hour after intraperitoneal injection of 20 mg./Kg. of the four potentiating agents. Figure 6 presents the changes in blood pressure recorded following administration of 0.2 mg./Kg. of reserpine alone and after pretreatment with the four potentiating agents.

Discussion

This investigation was primarily concerned with an evaluation of the interaction of four synthetic compounds of diverse structure (SKF 525-A, Lilly 18947, NDR A-1358, and NDR A-2435) reported to enhance markedly the effects of certain drugs in doses which alone exert little or no pharmacologic activity, and six hypotensive agents which have essentially different mechanisms of depressor action (reserpine, rescinnamine, hydralazine, mecamylamine, an experimental benzodioxan derivative, and mannitol hexanitrate).

The depressor response to each of the six hypotensive drugs was significantly ($P<0.001$) increased by prior administration of the four potentiating agents in doses which alone produced no detectable change in the systolic blood pressure of hypertensive rats. An average increase of approximately 100 per cent in the depressor activity was observed in rats pretreated with potentiating agents. Ratios of 1.7 to 2.5 were obtained by comparing total systolic blood pressure reduction (sum of the changes in systolic pressure determined 1, 2, 4, and 6 hours after intraperitoneal injection of the hypotensive drug) in the group pretreated with potentiating agent to the total reduction in the group pretreated only with solvent (described in the section on methods).

Comparable enhancement of the depressor activity of hydralazine, mecamylamine, the benzodioxan compound NDR A-2275, and mannitol hexanitrate by the four potentiating agents was observed in normotensive dogs. The marked central nervous system depression produced in dogs by reserpine and rescinnamine after administration of the potentiating agents led us to discard the data obtained with these alkaloids in this phase of the investigation.

Several investigators (7, 8, 9) have studied the inhibitory effect of SKF 525-A and Lilly 18947 on a variety of drug metabolic pathways *in vitro* and *in vivo*. Fouts and Brodie (7) concluded that these synthetic compounds, despite their dissimilarity in structure, both

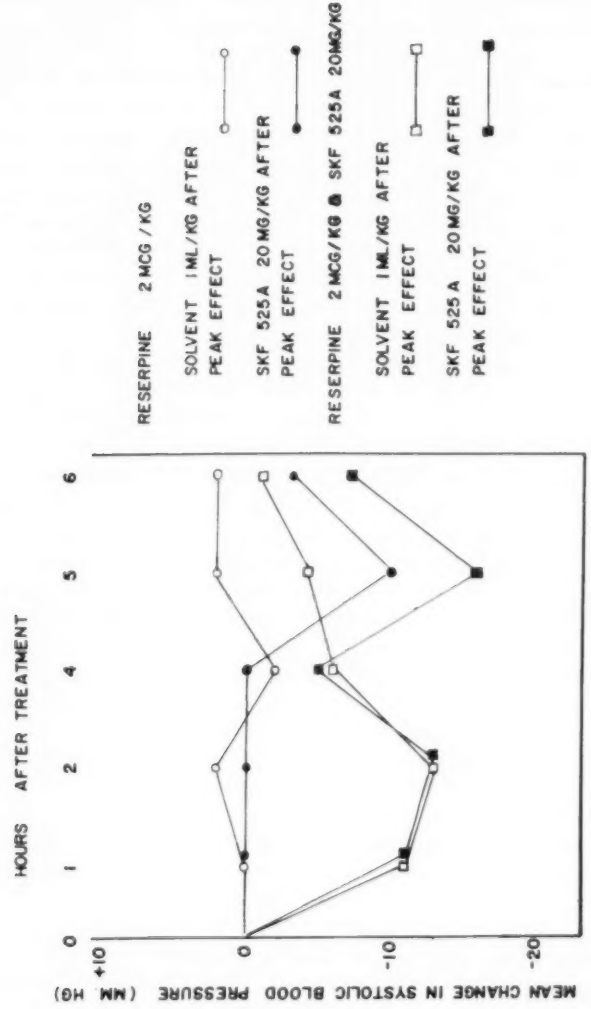
RESERPINE 2 MCG / KG
SOLVENT 1 ML/KG AFTER
PEAK EFFECT
SKF 525A 20 MG/KG AFTER
PEAK EFFECT
RESERPINE 2 MCG/KG & SKF 525A 20MG/KG
SOLVENT 1 ML/KG AFTER
PEAK EFFECT
SKF 525A 20MG/KG AFTER
PEAK EFFECT
MEAN CHANGE IN SYSTOLIC BLOOD PRESSURE (MM. HG)
+10
0
-10
-20
HOURS AFTER TREATMENT
0
1
2
4
5
6

FIGURE 4

enhance the activity of various classes of drugs by inhibiting the enzyme systems present in liver microsomes which are responsible for the biotransformation of the drugs investigated. It was recently shown by these investigators (10) that the reductive system occurring in the soluble fraction of the liver cell was considerably more sensitive to the blocking effect of SKF 525-A than the reductase present in the microsomes. This observation indicates that both enzyme systems may be involved in the mechanism of action of SKF 525-A. Maass *et al.* (11) reported that SKF 525-A retards the rate at which mephenesin is metabolized. Axelrod *et al.* (8) have indicated that the prolongation of barbiturate-induced hypnosis by SKF 525-A is due to an inhibition of side chain oxidation. This compound was also reported, by these investigators, to inhibit the demethylation of meperidine, aminopyrine, and ephedrine.

Our data concerning the enhancement of the effect of various hypotensive drugs, together with certain observations of investigators regarding other classes of drugs, suggest that the mechanism of the enhancing effect of SKF 525-A and other compounds which manifest similar degrees of potentiating activity cannot be explained solely on the basis of retarding the rate of metabolic degradation of the drug in question. The fact that potentiating agents prolong the duration of action of various types of drugs, including hypotensive agents, supports the theory that the rate of biotransformation of such drugs is decreased. However, the following observations suggest that other mechanisms, not fully revealed at present, must also be operative: a. SKF 525-A prolongs hexobarital-induced hypnosis in mice without significantly altering the LD_{50} of the barbiturate (12); b. The analgesic activity but not the respiratory depressant or toxic effect of morphine is enhanced by SKF 525-A (13); c. Anticonvulsant potency and neurotoxicity are not uniformly increased by SKF 525-A (14); d. Injection of SKF 525-A in the sciatic nerve-gastrocnemius muscle preparation of the chloralosed dog, after the curarizing action of succinylcholine had ceased, resulted in a renewed and substantially increased curarizing effect (15, 16). These investigators are of the opinion that the influence of SKF 525-A on the curarizing activity of succinylcholine may be attributed to displacement of the neuromuscular blocking agent fixed in an active form on non-specific receptors.

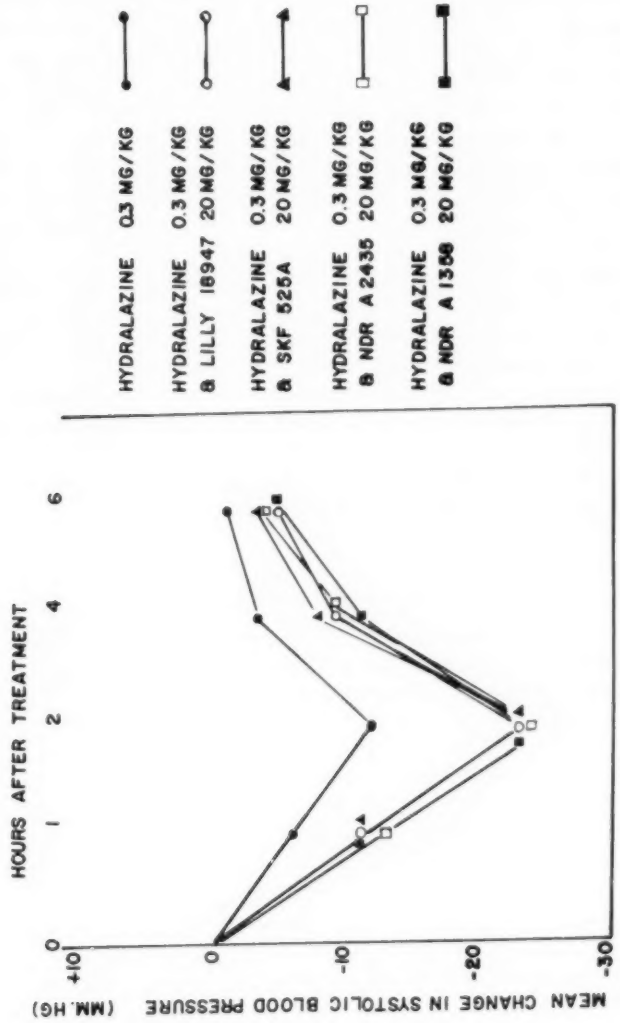
HYDRALAZINE 0.3 MG/KG
HYDRALAZINE 0.3 MG/KG
& LILLY 18947 20 MG/KG
HYDRALAZINE 0.3 MG/KG
& SKF 525A 20 MG/KG
HYDRALAZINE 0.3 MG/KG
& NDR A 2435 20 MG/KG
HYDRALAZINE 0.3 MG/KG
& NDR A 1358 20 MG/KG
HOURS AFTER TREATMENT
0
1
2
4
6
MEAN CHANGE IN SYSTOLIC BLOOD PRESSURE (MM. HG)
+10
0
-10
-20
-30

FIGURE 5

Two different types of experiments performed during the course of this investigation indicate that a similar mechanism may be operative insofar as the potentiation of hypotensive drug activity is concerned. It was shown, in unanesthetized hypertensive rats, that a renewed and sharply defined depressor response was elicited by administration of either SKF 525-A, Lilly 18947, NDR A-1358, or NDR A-2435 after the blood pressure reducing effect of various hypotensive drugs had largely terminated. In most instances, the second fall in blood pressure occurring after injection of non-depressor doses of the four potentiating agents was substantially greater than the initial reduction produced by the hypotensive drug alone. It was also observed that subthreshold doses of the hypotensive drugs evoked a significant decrease in blood pressure when administered to hypertensive rats or normotensive dogs after treatment with any of the four previously mentioned potentiating agents.

Although the mechanisms of potentiation remain to be established, these studies suggest that SKF 525-A and certain other synthetic compounds which enhance drug activity (Lilly 18947, NDR A-1358, and NDR A-2435) may have more than a single mode of action based on the inhibition of drug metabolic pathways.

Acknowledgment

For valuable assistance in design of the experiments and statistical analysis of the data, the authors are grateful to Joseph L. Ciminera of Merck Sharp and Dohme, Inc.

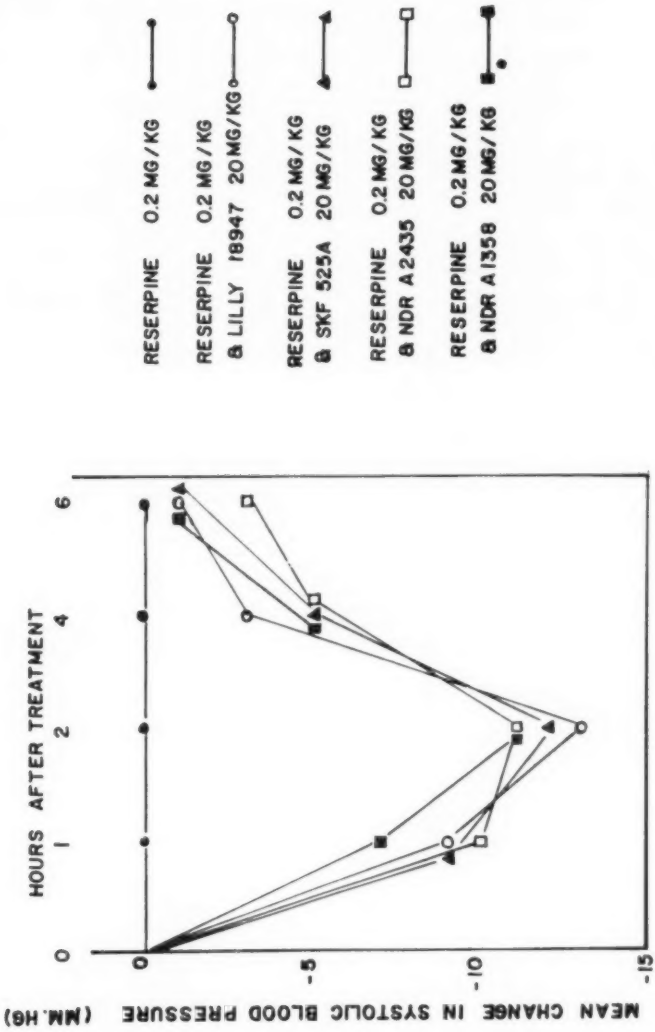
RESERPINE 0.2 MG/KG
RESERPINE 0.2 MG/KG
& LILLY 18947 20 MG/KG
RESERPINE 0.2 MG/KG
& SKF 525A 20 MG/KG
RESERPINE 0.2 MG/KG
& NDR A 2435 20 MG/KG
RESERPINE 0.2 MG/KG
& NDR A 1358 20 MG/KG
HOURS AFTER TREATMENT
0
1
2
4
6
0
-5
-10
-15
MEAN CHANGE IN SYSTOLIC BLOOD PRESSURE (MM. HG)

FIGURE 6

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REPORT OF AN INVESTIGATION OF D-PROPOXYPHENE HYDROCHLORIDE *

By J. W. Marrs, W. W. Glas, and J. Silvani

THE purpose of this investigation was to evaluate the drug, D-Propoxyphene Hydrochloride (α-d-4-dimethylamino-1, 2-diphenyl-3-methyl-2-proprionoxybutane hydrochloride) as compared with other analgesics including codeine phosphate, acetylsalicylic acid, and a placebo. Six unknown medications were used. These were known to us only by code letters A, B, C, D, E, and F. All the capsules were identical in appearance. None of the investigators knew the code. The method used for evaluating the effectiveness of the drug will be described below.

Method

Patients were selected who appeared mentally competent and complained of pain which had previously been treated with oral medications or hypodermic analgesics. Analgesics, sedatives, tranquilizers, and narcotics were restricted between the hours of 8:00 P. M. and 4:00 A. M. for the two days of the study. The unknown drugs were given at 8:00 A. M., 12:00 noon, and 4:00 P. M.

The unknown drugs were as follows:

A. ASA Compound (acetylsalicylic acid 227 mg., acetophenetidin 162 mg., and caffeine 32.4 mg.)

B. D-Propoxyphene Hydrochloride 65 mg.

C. Codeine sulfate 32 mg.

D. Placebo

* From the Department of Surgery, Wayne County General Hospital, Eloise, Mich.

E. D-Propoxyphene Hydrochloride 32 mg. with acetylsalicylic acid 227 mg. (3½ gr.), acetophenetidin 162 mg. (2½ gr.), and caffeine 32.4 mg. (½ gr.).

F. Acetylsalicylic acid 333 mg. (5 Gr.).

The drugs were given in a randomized order so that each patient received one dose of the six basic test drugs. Randomization provided that in every instance each drug was preceded by and followed by all of the test drugs a comparable number of times. The special nurse administered the drugs, and the relief of pain afforded by each drug was evaluated four hours following the administration of the drug. The degree of relief of pain was reported for each unknown by assigning it a number from 1 through 5. The therapeutic effectiveness code reading as follows: No. 1—no relief, No. 2—poor relief, No. 3—fair relief, No. 4—good relief, and No. 5—excellent relief. The duration of analgesia was recorded as being from 0 to 4 hours. A total of 54 studies were done. Of these, 44 were men and 10 were women. Ages ranged from 19-78, the majority being in their late forties and fifties. Most of the patients had less than a high school education and many were indigent.

Both acute pain and chronic pain were evaluated and types of pain evaluated included such etiologies as postoperative mastectomies, recurrent joint pain of the shoulder secondary to bursitis, pain following a ganglionectomy for tic douloureux, chronic osteomyelitis of the leg and toe, abdominal pain of unproven etiology but probably secondary to carcinoma of the pancreas, pain in a postoperative skin graft to the axilla, painful swelling of the mandible secondary to carcinoma of the tongue, leg pains in a partial paraplegic patient, abdominal pains secondary to carcinoma of the rectum, pain secondary to Buerger's disease of the feet and hands, postoperative lobectomy for bronchiectasis, and many other postoperative conditons. There were numerous instances of pain secondary to carcinoma involving both bony and soft tissues. There were several instances of pain in the joints secondary to rheumatoid arthritis.

TABLE 1

D-PROPOXYPHENE HYDROCHLORIDE

THERAPEUTIC EFFECTIVENESS

	1	*2*	*3*	*4*	*5*		
Drug	*No Relief*	*Poor Relief*	*Fair Relief*	*Good Relief*	*Ex-cellent Relief*	*No. Times Drug Adm.*	*Duration of Analgesia*
A Acetylsalicyclic Acid, Acetophenetidin, and Caffeine Compound	12	14	14	11	2	53	3.64 hours
B D-Propoxyphene Hydrochloride 65 mg.	15	14	16	8	1	54	3.66 hours
C Codeine 32 mg.	17	6	23	8	0	54	3.68 hours
D Placebo	17	10	11	11	4	53	3.38 hours
E D-Propoxyphene Hydrochloride Compound (D-Propoxyphene Hydrochloride 32 mg. with Acetylsalicylic Acid, Acetophenetidin and Caffeine Compound)	6	2	8	22	16	54	3.76 hours
F Acetylsalicylic Acid 5 gr.	12	6	11	18	6	53	3.55 hours

Note: 55 patients given drugs (if patient given drugs twice, he is counted as two patients).

Evaluation and Results

Fifty-four studies were completed. Table 1 summarizes the response of these cases to the analgesics. Table 2 rates the analgesic potency of the various drugs using fair, good, or excellent relief as

criteria. Table 3 rates them according to criteria of good and excellent relief. The duration of analgesia of each drug was included in Table 1. No patients reported any undesirable effects from the drugs. No toxic or undesirable side effects were noted by the participating physicians.

TABLE 2

D-PROPOXYPHENE HYDROCHLORIDE

Drug	*Number of times Fair, Good, or Excellent Relief was obtained*	*Rating*
A Acetylsalicylic Acid, Acetophenetidin, and Caffeine Compound	27	4th
B D-Propoxyphene Hydrochloride 65 mg.	25	6th
C Codeine 32 mg.	31	3rd
D Placebo	26	5th
E D-Propoxyphene 32 mg. with Acetylsalicylic Acid, Acetophenetidin, and Caffeine Compound	46	1st
F Acetylsalicylic Acid gr. 5	35	2nd

Discussion

The results indicate that Dextro-Propoxyphene with Acetylsalicylic Acid, Acetophenetidin, and Caffeine are significantly better than the blank. The other analgesics are not significantly different from the placebo or from each other. The duration of analgesia would not appear significant.

TABLE 3

D-Propoxyphene Hydrochloride

Drug	*Number of times Good and Excellent Relief was obtained*	*Rating*
A Acetylsalicylic Acid, Acetophenetidin, and Caffeine Compound	13	4th
B D-Propoxyphene Hydrochloride 65 mg.	9	5th
C Codeine 32 mg.	8	6th
D Placebo	15	3rd
E D-Propoxyphene Hydrochloride 32 mg. with Acetylsalicylic Acid, Acetophenetidin, and Caffeine Compound	38	1st
F Acetylsalicylic Acid gr. 5	24	2nd

These results, on first inspection, may seem confusing since the placebo is rated superior to codeine. This is not unusual. Beecher (1) was unable to distinguish between morphine 10 mg., codeine 60 mg., phthalmide, and a placebo when these drugs were administered *orally*. Narcotics, given orally, are relatively ineffective (2, 3) and are generally inferior to acetylsalicylic acid 600 mg. (1). In addition, the "placebo reactors" were not identified and excluded from this study.

Conclusions

Six unknown drugs were tested to determine the effectiveness of D-Propoxyphene Hydrochloride as compared to other oral analgesics. Drug F, Acetylsalicylic Acid, and drug E, D-Propoxyphene Hydrochloride Compound combining D-Propoxyphene Hydrochloride with Acetylsalicylic Acid, Acetophenetidin, and Caffeine, were statistically better than the placebo. Significant differences between the remaining drugs were not obtained in this series of 54 patients. The low level of education of the patients is probably the main factor contributing to errors in this study, most having less than a high school education and many being indigent county hospital invalids.

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SELECTED ABSTRACTS

Aluminum Allantoinates in Dermatological Applications. Lubowe, I. I. and Mecca, S. B. *Drug and Cosm. Ind. 84*:36 (1959). Allantoin has proven to be an effective topical agent for the promotion of healing and to have keratolytic and anti-irritant properties as well. Aluminum derivatives of allantoin have recently been developed in an effort to combine the properties of allantoin with the astringent and bacteriostatic activity of aluminum. Two such compounds and some of their clinical properties were described by the authors.

Aluminum chlorhydroxy allantoinate [$Al(OH)_4ClC_4H_5N_4O_3$] is soluble in about 55 parts of water and in 200 parts of alcohol, the pH of a saturated solution in water being about 4.7. Aluminum dihydroxy allantoinate [$Al(OH)_2C_4H_5N_4O_3$] is insoluble in water and alcohol, the pH of a 4 per cent suspension in water being about 7.5.

Aluminum chlorhydroxy allantoinate has been found to be an effective deodorant, mild astringent, anti-irritant, and a healing stimulant. It may be used alone as a deodorant or as an additive to antiperspirant-deodorant preparations in a concentration of 0.25 per cent. It was non-irritating and actually reduced the potentially irritating properties in preparations in which it was an additive. In triethanolamine lotions used for the treatment of acne vulgaris, a 2 to 4 per cent concentration, without sulfur and other ingredients frequently included in such preparations, the acne lesions were observed to dry and relief was obtained from itching and erythema. In a particular study of the deodorant properties of this compound, complete relief from odor was obtained for a period of 24 hours after application.

Aluminum dihydroxy allantoinate was found to have mild antiperspirant and anti-eczematous properties. In lotions, creams, and dusting powders, it was found to be effective against diaper dermatitis because of its acid- and ammonia-consuming properties. In a cream, it was also found to be effective in the prophylaxis and treatment of dermatitis venenata due to soap, water, alkalies, and detergents.

No evidence of primary irritation or sensitization was observed in the many cases treated with these compounds.

The Preservation of Food for the Armed Forces By Irradiation. Goresline, H. E. and Desrosier, N. W. *Am. J. Public Health 49:*488 (1959). To meet the challenge of supplying food to the highly mobile armed forces in modern warfare on land, in the air, on the sea, or under the sea and to provide it light in weight, small in size, stable without refrigeration, nutritious and palatable, new methods of food preparation and preservation are being investigated. The authors described some of the problems encountered and the studies being continued in the preservation of food by irradiation sterilization.

To insure preservation of foods, there must be assurance that all of the microorganisms causing deterioration and spoilage are destroyed. *Clostridium botulinum* has been found to be the most difficult food-contaminating microorganism to kill, requiring about 4.5 million rads in foods above pH 4.5 as compared with about 250,000 rads for most vegetative molds and yeasts and 3 to 4 million rads for most spore-forming bacteria. Considerable progress has been made in developing chemical dosimeters to indicate the amount of energy absorbed by a given package of food and indicators to show that a given package has been irradiated. These are used in conjunction with radiation monitors. It has also been found that larger doses of radiation are required to inactivate the natural enzymes of plant and animal tissue than to destroy microorganisms. Since adverse flavor and texture changes increase as the radiation dose increases, studies are being undertaken to inactivate the enzymes by low-level heating and then destroy the microorganisms by irradiation.

Higher levels of irradiation have been found to cause changes in flavor and texture of certain foods. Beef has been found to change in flavor appreciably. The packaging of the food in flexible films has also introduced problems. The films have sometimes been found to evolve odors during irradiation and to show cracking and other evidences of instability.

Limited studies on the acceptability of the irradiated foods have been completed with encouraging results. Extensive studies are in progress to determine the wholesomeness of the irradiated foods. Both short-term and long-term feeding studies are in progress on several species of animals. The authors emphasized that it is essential to prove that the consumption of radiation sterilized foods cause no untoward physiologic response, are nutritionally adequate, are not carcinogenic, and do not cause adverse changes in enzyme systems.

An Evaluation of Sustained Release From Pelleted Preparations. Shenoy, K. G., Chapman, D. G., and Campbell, J. A. *Drug Standards 27:77* (1959). The evaluation of sustained-release preparations has been subject to considerable variation and uncertainty. The authors attempted to approach the problem by the use of data obtained from urinary excretion, physiological availability *in vivo,* and the rate of release *in vitro.* Amphetamine was used as the medication. Eight commercially available pelleted preparations of the sustained-release type were evaluated.

Nine normal male volunteers were used for the *in vivo* testing. For each subject, data were obtained on a blank urinary excretion prior to the ingestion of the drug, on the urinary excretion following the ingestion of the pure drug in solution (considered to be totally available), and on the urinary excretion following the ingestion of the sustained-release capsules. The *in vitro* studies were performed in 4 oz. bottles containing artificial gastric juice for 30 minutes and then artificial intestinal juice. The contents of the capsules were placed in the bottles and then revolved end over end at 12 r.p.m. in a bath at 37° C.

The pure excretion of *d*-amphetamine following the ingestion of the pure solution was 52.2 per cent, and of *dl*-amphetamine was 69.8 per cent. It was assumed that the drug was totally available from the solution. Thus, these excretion values were considered to represent that obtained from the totally available drug. The urinary excretion rate curves were expected to show a constant excretion rate for the drug for several hours if a sustained-release effect was obtained.

Evaluation of the results indicated that only two of the preparations showed constant urinary excretion at an adequate level and were also quantitatively available. Three preparations were available but did not show constant excretion, one showed constant excretion but was not available, and two were both not available and did not show constant excretion. One hour *in vitro* release data correlated well with urinary excretion rates.

The authors concluded that it would appear to be possible to develop a relationship between *in vitro* testing methods, such as the one employed in these tests, with *in vivo* effects to show whether or not a product has sustained action *in vivo.* They also concluded that considerable differences can be expected in the clinical effect from sustained-release products presently on the market.

BOOK REVIEW

Biochemistry and Human Metabolism, Third edition. B. S. Walker, W. C. Boyd, and I. Asimov. vii + 937 pp. The Williams and Wilkins Co., Baltimore 2, Md., 1957. Price: $12.00.

As the title indicates, the object of this book is to relate chemistry and metabolism in the human body. The twenty-two chapters are broken down into five main topics: Structure, Control, Growth, Metabolism, and Pathology. Many of the chapters of the two previous editions have been expanded and, in a few cases, split into two to allow for a better division of the subject matter. Much of the material is of very recent vintage such as is contained in the chapters on Cancer, Enzymes and Enzyme Systems, and an Appendix on the effects and uses of radioisotopes. This is much more than a text—it is even more than a reference work since it reads very easily besides being a concentrated source of a host of biochemical information. Each chapter is well supplied with references, and a liberal index (40 pages) makes this a most valuable addition to any scientific library.

A. R. GENNARO

American Journal of Pharmacy

The American Journal of Pharmacy is the oldest continuously published scientific periodical of its kind in America, having been established by the Philadelphia College of Pharmacy in 1825. After the original issue there were three other preliminary numbers until 1829, when regular publication began. From then until 1852 four issues were published annually, with the single exception of 1847, when an additional number appeared. Six issues a year were printed from 1853 to 1870, at which time the Journal became a monthly publication.

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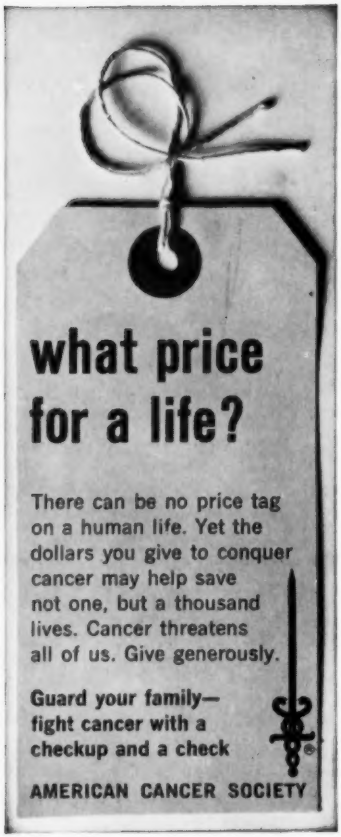
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